REMARKS

Applicants thank the Examiner for the telephone interview conducted on December 22, 2009. Applicants have carefully considered the October 2, 2009 non-final Office Action, and submit that the subject application is in condition for allowance based upon the amendments made herein and the following remarks.

Status of the Claims.

On April 24, 2004, Applicants filed the subject application. The subject application was originally filed with 24 claims. On August 14, 2006, Applicants filed a First Preliminary Amendment, amending the subject application to add claims 25-33. On March 5, 2007, the Office issued a Restriction Requirement. On April 5, 2007, Applicants provisionally elected, with traverse in part, to prosecute claims 25-33. Applicants traversed the restriction with respect to claims 1-14 and, in a May 9, 2007 Office Action, the Office rejoined claims 1-14. On August 9, 2007, Applicants canceled claims 5 and 12-24. By this amendment, Applicants amend claims 1, 3, 25, 27, 31, and 33. Claims 1-4, 6-11, and 25-33 remain pending in the subject application.

Summary of the Office Action

In the October 2, 2009 non-final Office Action, the Office:

(1) objected to claims 27 and 33 and required correction of Applicants' nomenclature of the substance corresponding to DSPE-MPEG2000;

(2) rejected claims 27 and 33 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, on the ground that Applicants' nomenclature of the substance corresponding to DSPE-MPEG2000 requires correction;

(3) rejected claims 1-6, 10, 25, and 28-31 under 35 U.S.C. 102(b) as anticipated by "newly found prior art,"[1] specifically U.S. Patent No. 6,468,505 issued to Lang et al ("Lang");

(4) rejected claims 1, 6-8, 10, 25, and 28-31 under 35 U.S.C. 102(b) as anticipated by Lang as evidenced by U.S. Patent No. 5,204,085 issued to VanDeripe ("VanDeripe"); and

(5) rejected claims 1-4, 6-11, and 25-33 under 35 U.S.C. 103(a) as being unpatentable over Lang in view of U.S. Patent No. 5,676,928 issued to Klaveness ("Klaveness") and further in view of Leike et al., Invest. Radiol. 2001, 36, 303-308 ("Leike").

For the reasons set forth below, Applicants submit that the Office should withdraw its objection to claims 27 and 33 and the rejection of claims 1-4, 6-11, and 25-33, and allow those claims.

1. Objection to claim 27 and 33 as requiring correction of Applicants' nomenclature of the substance corresponding to DSPE-MPEG2000.

The Office correctly points out that DSPE corresponds to 1,2-distearoyl-sn-glycerol-3-phosphoethanolamine. Applicants have amended claims 27 and 33 to recite N-carbamylmethoxypoly(ethylene glycol)-1,2-distearoyl-sn-glycerol-3-phosphoethanolamine (DSPE-MPEG2000). Thus, the Office's objection to those claims has been addressed and should be withdrawn.

[1] At the outset, Applicants disagree with the Office's characterization of Lang as "newly found prior art." The Supervisory Patent Examiner in this case is Michael G. Hartley. Supervisory Patent Examiner Hartley was the Primary Examiner of the U.S. patent application (Appl. No. 09/696,352) that matured into the Lang patent. Thus, Supervisory Patent Examiner Hartley has been aware of Lang since before the filing date of the subject application. Yet, Lang was not "found" in any of the three prior Office actions, or in the Examiner's Answer on the first appeal of the subject application.

2. Rejection of claims 27 and 33 under 35 U.S.C. § 112, second paragraph.

As set forth above, Applicants have amended claims 27 and 33 to recite N-carbamylmethoxypoly(ethylene glycol)-1,2-distearoyl-sn-glycerol-3-phosphoethanolamine (DSPE-MPEG2000). Thus, the Office's rejection of those claims under 35 U.S.C. § 112, second paragraph, has been addressed and should be withdrawn.

3. Rejection of claims 1-6, 10, 25, and 28-31 under 35 U.S.C. 102(b) as anticipated by Lang.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. M.P.E.P. § 2131.

Applicants have amended claim 1 to recite: "liposomes, the liposomes encapsulating one or more iodinated nonradioactive contrast-enhancing agents." Lang does not teach iodinated nonradioactive contrast-enhancing agents. As such, Lang does not anticipate amended claim 1.

Similarly, Applicants have amended claim 25 to recite: "the liposomes encapsulate at least one iodinated nonradioactive contrast enhancing agent." Again, Lang does not teach iodinated nonradioactive contrast enhancing agents. As such, Lang does not anticipate amended claim 25.

Claims 2-6 and 10 depend directly or indirectly from claim 1. Claims 28-31 depend directly or indirectly from claim 25. Dependent claims are construed to include all of the limitations of the "parent" claim. These limitations are considered to be incorporated by reference into the dependent claims. 35 U.S.C. § 112, ¶ 4. Thus, Lang necessarily fails to disclose each and every limitation of claims 2-6, 10, and 28-31 as well.

For the forgoing reasons, Applicants submit that the Office should withdraw the rejection of claims 1-6, 10, 25, and 28-31 under 35 U.S.C. § 102(b) as being anticipated by Lang.

4. Rejection of claims 1-6, 10, 25, and 28-31 under 35 U.S.C. 102(b) as anticipated by Lang as evidenced by VanDeripe.

As set forth above, Lang does not anticipate amended claims 1 and 25, or their respective dependent claims (claims 2-6, 10, and 28-33). VanDeripe does not provide the missing teachings. Thus, Applicants submit that the Office should withdraw the rejection of claims 1-6, 10, 25, and 28-31 under 35 U.S.C. § 102(b) as being anticipated by Lang as evidenced by VanDeripe.

5. Rejection of claims 1-4, 6-11, and 25-33 under 35 U.S.C. 103(a) as being unpatentable over Lang in view of Klaveness and further in view of Leike.

a. Principles of Law.

The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *see also* September 10, 2009 Decision on Appeal, Appeal No. 2009-003511 ("Decision"), at p. 7.

While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.; see also* Decision, at p. 7. "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008); *see also* Decision, at p. 7.

Moreover, an obvious to try rationale (whether or not explicitly denominated as such) for supporting an obviousness rejection may be improper in certain situations. Decision, at p. 7. The Court of Appeals for the Federal Circuit set forth in *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), two situations in which an "obvious to try" rationale is improperly applied. Most pertinent to the October 2, 2009 non-final Office Action is the situation of "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters are critical or no directions as to which of many possible choices is likely to be successful." *Id.*; *see also In re Kubin*, 561 F.3d 1351, 1358-60 (Fed. Cir. 2009) (noting that the rationale in *O'Farrell* was "affirmed in the logical inverse" in *KSR*, 550 U.S. at 417, in the statement that "§103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'"); Decision, at p. 7.

b. The Claims and the Cited References.

As amended, Claim 1 recites liposomes comprising cholesterol, at least one phospholipid, and at least one phospholipid that is derivatized with a polymer chain, wherein the liposomes encapsulate one or more iodinated nonradioactive contrast-enhancing agents, and wherein the average diameter of the liposomes is less than 150 nanometers. As amended, Claim 25 is drawn to a liposome composition comprising a lipid or phospholipid, at least one second lipid or phospholipid which is derivatized with one or more polymers, and at least one sterically bulky excipient capable of stabilizing the liposomes, wherein the average diameter of the liposomes is less than 150 nanometers, and wherein the liposomes encapsulate at least one iodinated nonradioactive contrast enhancing agent.

As its principal reference against claims 1 and 25, the Office asserts Lang. Lang teaches Gadolinium complexes as contrast agents. Lang mentions the gadolinium complexes' use in liposomes for, among other diagnostic techniques, computed tomography, *see* Lang at Abstract.

However, Lang does not provide a single example of such a use. Instead, Lang *solely* demonstrates the use of such complexes in magnetic resonance imaging. *See* Lang, col. 5, ll. 31-32.

Applicants and the Office agree that Lang does not teach iodinated nonradioactive contrast-enhancing agents. *See* October 2, 2009 non-final Office Action, at p. 7. Thus, the Office once again[2] asserts that a reference it contends teaches all of the elements of the claimed compositions, including the average diameter of the liposomes being less than 150 nm, *except for the iodinated nonradioactive contrast agent*.

To fill this void, the Office again[3] asserts Klaveness, this time as a combination reference. Klaveness teaches iodinated nonradioactive contrast-enhancing agents as X-ray contrast agents. Klaveness does not teach or suggest a liposome composition comprising a sterically bulky excipient (i.e., cholesterol). And, while Klaveness makes a passing (and non-enabling) statement that "compositions of the invention, for use in any type of imaging, may if desired be modified with materials such as polyethylene glycol to increase the circulation half-life of the liposomes," Klaveness, col. 11, ll. 7-11, Klaveness does not provide a single example of a liposome (of any size) that includes such a modification, and does not state or imply that the size of such a modified liposome would or could remain in the pertinent average size range of amended claims 1 and 25 (i.e., less than 150 nm).

Klaveness also teaches heavy metal cluster/chelate X-ray contrast agents. However, Klaveness does not provide a single example of such a use. Instead, Klaveness *solely* demonstrates the use of such complexes in magnetic resonance imaging. Indeed, notwithstanding the Office's strikingly advocative contention to the contrary, *see* the October 2,

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[2] *See* Decision, at p. 10 ("We agree with the Examiner that Torchilin teaches all of the elements of the composition, including the average diameter of the liposomes being less than 150 nm, except for the nonradioactive contrast-enhancing agent.")

[3] *See* May 5, 2007 non-final Office Action, wherein the Office rejected claims 1 and 25 under 35 U.S.C. § 102(b) as anticipated by Klaveness. The Office later withdrew Klaveness altogether.

2009 non-final Office Action, at p. 8, Klaveness does ***not*** categorize the Gd-DTPA-BMA contrast agents of Lang and the iodinated X-ray contrast agents of Klaveness "as *equivalent imaging agents/contrast agents*." (Emphasis added.) In fact, Klaveness consistently distinguishes compositions for use as X-ray contrast agents, such as iodinated contrast agents, from compositions for use as MRI contrast agents, such as gadolinium complexes. *See, e.g.*, Klaveness, at col. 1, ll. 14-39 (discussing "X-ray imaging, including applications such as computed tomography (CT)") compared to col. 1, l. 61 – col. 2, l. 34 (discussing "MR contrast agents"); and col. 4, l. 44 – col. 5, l. 10 (discussing "Compositions of the invention for use in X-ray imaging") compared to col. 5, ll. 11-58 (discussing "Compositions of the invention for use in MR imaging"); and col. 10, ll. 4-23 (discussing "iodinated X-ray contrast agent") compared to col. 10, ll. 24-32 (discussing "Liposome compositions for MR imaging"); and Example 1 ("Encapsulation of X-ray Imaging Agent") compared to Example 11 ("MR Contrast Agent").

Significantly, the Office does not offer a single reference that provides any reason or rationale of *how* to combine the liposomes of Lang with the liposomes of Klaveness in a manner that would lead to the claimed liposome compositions.

c. Analysis.

The Office's logic in the October 2, 2009 non-final Office Action may be summed up as follows:

(1) The Lang liposomes comprise a phopholipid, a derivatized phospholipid, and cholesterol. And the Lang liposomes maintain the claimed size. But the Lang liposomes comprise a gadolinium contrast agent.

(2) The Klaveness liposomes comprise a phospholipid. The Klaveness liposomes also comprise an iodinated non-radioactive contrast enhancing agent.

(3) Thus, it would be obvious to try to substitute the iodinated non-radioactive contrast enhancing agent of Klaveness for the gadolinium contrast agent of Lang and maintain the appropriate size.

This logic is indistinguishable from the Office's logic already presented to, and overruled by, the Board of Patent Appeals and Interferences (the "Board") in the first appeal of the rejection of claims 1 and 25:

(1) The Torchilin (Biochim. Biophys. Acta 1996, 1279, 75-83) liposomes comprise a phopholipid, a derivatized phospholipid, and cholesterol. And the Torchilin liposomes maintain the claimed size. But the Torchilin liposomes comprise NGPE-Fab contrast agents.

(2) The Sachse (Invest. Radiol. 1197, 32, 44-50) liposomes comprise a phospholipid. The Sachse liposomes also comprise an iodinated non-radioactive contrast enhancing agent.

(3) Thus, it would be obvious to try to substitute the iodinated non-radioactive contrast enhancing agent of Sachse for the NGPE-Fab contrast agent of Torchilin and maintain the appropriate size.

The Office's logic fails now just as it did in the first appeal because the Office has, again, not offered a reference that provides any reason or rationale of *how* to combine the liposomes of Lang (Torchilin) with the liposomes of Klaveness (Sachse) in a manner that would lead to the claimed liposome composition. This is what the law requires: "[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention

was made, it may not be legally concluded that the compound itself is in the possession of the public." *In re Hoeksma*, 399 F.2d 269, 274 (CCPA 1968); M.P.E.P. § 2145.[4]

With respect to the Office's flawed logic, the Board has ruled clearly and concisely. The Examiner is bound by the Board's ruling:

> We agree with the Examiner that *Torchilin teaches all of the elements of the composition, including the average diameter of the liposomes being less than 150 nm, except for the nonradioactive contrast-enhancing agent.* However, *the other references* ***establish*** *that the size of the liposome* ***will*** *vary once you start changing its composition.*
>
> Thus, Payne teaches formation of liposomes containing a biologically active compound using a liposome-forming amphiphatic lipid and, optionally, an adjuvant, wherein the biologically active compound may be a contrast agent, and the adjuvant may be cholesterol. While Payne teaches that small sizes of less than 150 nm may theoretically be obtained, the smallest size actually obtained by Payne was 0.16 microns, and *that liposome did not contain a non-radioactive imaging agent, nor did it include a lipid or phospholipid that is derivatized with a polymer chain.*
>
> Sachse, in our opinion, is in fact the most relevant of the references. That reference, as set forth by the Examiner, teaches all of the limitations of claims 1 and 25, except for the size. *While the liposomes not derivatized with a polymer chain had a mean diameter of about 132 nm, when the liposomes were derivatized with DSPE-PEG, their size dramatically increased to 204 nm.* Finally, in Leike, the liposomes did not include a non-radioactive contrast enhancing agent, and had a mean particle size of 201 nm. Thus, *we agree with Appellants that* ***the references*** *relied upon, either alone, or in combination,* ***do not teach how to obtain a liposome composition as required by claim 1 and 25, wherein the average diameter of the liposomes is less than 150 nm.***
>
> We thus conclude that this is analogous to the first situation in *O'Farrell*, where application of an obvious-to-try rationale is improper. *The situation is one where*

[4] *See also In re O'Farrell*, 853 F.2d at 903 (holding that the claimed method would have been obvious over the prior art relied on because one reference contained a *detailed enabling methodology*, a suggestion to modify the prior art to produce the claimed invention, *and evidence suggesting the modification would be successful*).

> *the ordinary artisan would need to vary all parameters to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters are critical*[5] *or no direction as to which of many possible choices is likely to be successful.* ***The prior art demonstrates that the size of the liposomes is dependent on their composition***. And while Payne in particular may give some general guidance, as seen from Sachse, ***even adding one additional component, in that case, derivatizing with a polymer chain, can, in the words of the reference, result in "a drastic increase in vesicle size."*** In particular, *it appears as if the Examiner has found all of the pieces in the art, but provides no reason or rationale of how to combine them in [a] manner that would lead to the claimed liposome composition.*

Decision, at pp. 10-11 (emphasis added). Thus, the Board has unequivocally ruled that: (1) the size of the liposomes is dependent on their composition; and (2) simply finding the pieces of the claims in the art is not sufficient to establish obviousness in the absence of a reference specifically[6] demonstrating a "reason or rationale of *how* to combine them in [a] manner that would lead to the claimed liposome composition." *Id.* at p. 11 (emphasis added).

The October 2, 2009 non-final Office Action flouts the Board's ruling. First, nothing in Lang suggests that substituting the iodinated contrast enhancing agents of Klaveness for the gadolinium complexes of Lang will not also cause a "drastic increase in vesicle size." Certainly nothing in Lang teaches *how* one might accomplish that feat. Indeed, the Board has already expressly ruled in this case that the "*references* ***establish*** *that the size of the liposome* ***will*** *vary once you start changing its composition.*" Decision, at p. 10. Second, Klaveness does not demonstrate a liposome that comprises cholesterol or a derivatized phospholipid. And Klaveness does not state or imply that the size of the Klaveness liposomes would remain the same if cholesterol and a derivatized liposome were included. In fact, as the Board *has already*

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[5] In the October 2, 2009 non-final Office Action, the Office acknowledges this requirement without actually addressing it: "The size of the liposomes of Lang et al. are *critical* . . . ." October 2, 2009 non-final Office Action, at p. 8 (emphasis added). Obviously, the Board did not mean that a "critical" parameter in *achieving* the appropriate size of a liposome is the size of the liposome.

[6] The Board has already rejected the Office's approach of asserting a reference (Payne) that generally discusses the manipulation of liposome size. Decision, at p. 10.

expressly ruled in this case, the opposite is true: "While the liposomes not derivatized with a polymer chain had a mean diameter of about 132 nm, *when the liposomes were derivatized with DSPE-PEG, their size dramatically increased to 204 nm.*" Decision, at p. 10 (citing Sachse et al, Invest. Radiol. 1997, 32, 44-50) (emphasis added).[7] In other words, once again, "*it appears as if the Examiner has found all of the pieces in the art, but provides no reason or rationale of* ***how*** *to combine them in [a] manner that would lead to the claimed liposome composition.*" Decision, at p. 11 (emphasis added). The Board has already ruled that a showing of the type offered by the Office in the October 2, 2009 non-final Office Action is insufficient to establish obviousness.

For the foregoing reasons, the Office should withdraw the rejection of claims 1 and 25 under 35 U.S.C. 103(a) as being unpatentable over Lang in view of Klaveness. If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is also nonobvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). As such, claims 2-4, 6-11, and 26-33 are likewise not obvious. Thus, Applicants submit that the rejection of claims 1-4, 6-11, and 25-33 under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

Based on the amendments and arguments presented herein, Applicants submit that the subject application is in condition for allowance. While no additional fees are believed necessary, please charge any additional fees or credit any overpayments to Deposit Account No. 50-5078, referencing Attorney Docket No. 27428-4.

[7] The Office must consider the totality of the art. *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986) ("The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness."); M.P.E.P. § 2145(X)(D)(3).

Respectfully submitted,

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